REMARKS

With entry of this amendment, the claims pending for consideration are claims 1-17, 19, 23-42, 44, 48-57, 59-61 and 67-82, as amended. Claims 18, 20-22, 43, 45-47, 58 and 62-66 are cancelled. Claims 67-82 are newly added.

Reconsideration of the application, as amended, is respectfully requested.

Double Patenting Rejection

Claims 1, 19-21, 26 and 44-47 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application 10/041,363. Applicants request that this rejection be held in abeyance inasmuch as neither case currently contains any allowed claims. Once applicants are given an understanding of the allowable subject matter in both cases, applicants can better assess the propriety of the double patenting rejection and the need for a terminal disclaimer.

The Section 112 Rejections

Claims 1-25, 39-43, 45-47, 49, 50 and 52-66 are rejected under 35 U.S.C. § 112, paragraph 2, as being indefinite. In response to the various Section 112 rejections, applicants have amended the claims as detailed below. Some of the amendments are purely grammatical and are not specified in the summary text below.

Claim 1 is amended, *inter alia*, by deletion of the phrase "or a portion of said solution," and addition of the phrase "said liquid composition being stable at room temperature". The added phrase is fully supported by the specification, for example, at pages 4 and 46.

Claim 12 is amended to clarify that the human erythropoietin included in the claimed composition is produced by endogenous gene activation.

Claims 14 and 16 are amended to depend from claim 13 which specifies a human EPO having a sequence selected from SEQ ID:NO 1 or SEQ ID: NO 2.

Claims 15 and 40 are amended to refer only to the one species elected as a result of the requirement for restriction dated September 27, 2002.

Claim 18 is cancelled.

Claims 20 and 21 are cancelled and presented as new claim 67.

Claim 22 is cancelled and presented as new claim 68.

Claim 23 is amended to be an independent claim and to add reference to SEQ ID NO: 1 and SEQ ID NO:2 in lieu of "human erythropoietin," and to state that the claimed composition is stable at room temperature.

Claim 24 is amended to delete reference to a "residue" and to define k.

Claim 25 is amended to correct spelling of "wherein," delete reference to "the residue" and to define k.

Claim 26 is amended to provide that the claimed liquid pharmaceutical composition is stable at room temperature.

Claims 39 and 41 are amended and refer specifically to SEQ ID NO: 1 or SEQ ID NO: 2.

Claim 40 is amended to refer to one sequence modification as was required by the restriction requirement of September 27, 2002.

Claim 41 is amended to refer to a human EPO having a sequence selected from SEQ ID NO: 1 or SEQ ID NO: 2.

Claim 43 is cancelled.

Claim 44 is amended to include the phrase "glycoprotein product" after erythropoietin.

Claims 45-47 are cancelled.

Claim 48 is amended *inter alia* to refer specifically to SEQ ID NO: 1 or SEQ ID NO: 2.

Claims 49 and 50 are amended to clarify that P is the erythropoietin glycoprotein minus the amino group(s) that form an amide linkage with the linker. Claim 50 is also amended to correct the spelling of "wherein".

Claims 51, 54 and 56 are amended to specify which component is the multiply charged anion and which is the pharmaceutically acceptable buffer.

Claim 52 is amended to state that the composition further comprises methionine and a polyol. Support for this formulation is found on pages 26-27 of the specification.

Claim 53 is amended to clarify that mannitol is a specific polyol that can be included in applicants' compositions. Support for this amendment is found at page 27.

Claim 55 is amended to clarify that the composition further comprises methionine.

Claim 57 is amended to state that the composition further comprises mannitol methionine, and pluronic F68.

Claim 58 is cancelled and presented as new claims 77-82.

Claim 59 is amended to add "selected from".

Claims 60 and 61 are amended to add "having a" and "about".

Claims 62-66 are cancelled.

Claims 67-82 are newly added.

These amendments are fully supported by the specification and are not believed to introduce any new subject matter.

Applicants submit the foregoing amendments overcome the pending Section 112 rejections and request withdrawal of these rejections.

The Section 102 Rejections

Claims 1-4, 6, 7, 9-12, 26-29, 31, 32, 34-37, 54 and 62-64 are rejected s being anticipated by U.S. Patent No. 4,992,419 (Woog et al.). This rejection is traversed.

To render its EPO compositions storage stable, Woog's EPO compositions are lyophilised. At column 3, lines 24-30, Woog specifically states:

> "For the production of the preparations according to the present invention, all adjuvant materials are dissolved in the necessary amount of water, then the EPO preparation, which preferably has an activity of about 100,000 to 200,000 units/mg. protein, is admixed, sterile-filtered into appropriate ampoules, frozen in and gently lyophilised at a low temperature."

Thus, contrary to the assertions in the Office Action at page 6, Woog does not disclose liquid storage stable EPO compositions. In contrast, applicants' claimed erythropoietin glycoprotein containing compositions are stable at room temperature in liquid form. This renders applicants'

compositions much more administration-friendly as they do not necessitate the steps of reconstitution at the infusion site.

The rejection relies specifically on the formulation the data for which is summarized in Table 1 of Woog. However, in Example 6, column 6, lines 50-53, Woog indicates that the data in Table 1 is based on a lyophilisate. In fact, all of Woog's EPO examples are lyophilisates (see, e.g., Examples 2, 3, 4, 5, and 6).

Nothing in Woog suggests that his reconstituted liquid EPO compositions are storage stable. On the contrary, if they were, there would have been no need to first prepare lyophilisates.

Analogously, claims 1-9, 11, 12, 62-64 and 66 are rejected as being anticipated by WO 96/40073 (Zale et al.). This rejection is also traversed.

Zale is completely inopposite. Zale relates to a sustained release composition wherein particles of aggregation-stabilized, biologically active, EPO are dispersed in a polymeric matrix of a biocompatible polymer. See, e.g., page 2, lines 9-16. The EPO solution to which Zale refers is an anti-aggregation solution which is prepared prior to dispersing the EPO in the biopolymer. The anti-aggregation agent described in Zale (e.g., at page 5, lines 30 – page 6, lines 28, cited by the Examiner) has an effect which is totally inconsistent with applicants' formulations; that is, the Zale aggregation agent reduces the EPO solubility by precipitating the EPO from the aqueous solution. In contrast, applicants formulations retain biologically active, solubilized, non-precipitated EPO stable for several months at room temperature. See applicants' specification at paragraph 4 and Table 3.

In view of the above arguments and amendments, the Section 102 rejections are overcome in part and traversed in part and should be withdrawn.

The Section 103 Rejections

Claims 1-4, 6, 7, 9-13, 26-29, 31, 32, 34-38, 54 and 62-64 are rejected under 35 USC § 103(a) as being obvious over Woog, supra, in view of WO 92/06116 (Rosen et al.). This rejection is traversed.

For the reasons stated above, Woog does not teach or suggest a liquid erythropoietin glycoprotein–containing composition that is storage stable at room temperature. Rosen's disclosure of the amino acid sequence of recombinant human EPO does not make up for the deficiencies of the primary reference, Woog. Woog, alone or in conjunction with Rosen, does not disclose applicants' specific liquid erythropoietin-containing compositions that are stable at room temperature without the use of serum albumin as an additive. See, e.g., the instant application at paragraphs 4, 8, and Table 3.

In addition, claims 1-4, 6, 7, 9-12, 14-17, 26-29,32, 34-37, 39-42, 54 and 62-64 are rejected under 35 USC § 103(a) as being obvious over Woog in view of EP 0640619 (Elliot). This rejection is also traversed.

Elliot is cited for disclosing EPO analogs having at least one additional glycosylation site. For the reasons provided above, Woog does not teach or suggest applicants' claimed liquid erythropoietin glycoprotein-containing composition that are stable at room temperature. Thus,

regardless of whether the EPO is unmodified or modified, the EPO formulations of Woog are not suggested to be liquid compositions that are storage stable at room temperature.

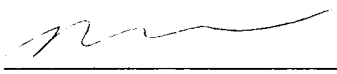
The Section 103 rejections are also overcome and should be withdrawn.

Furthermore, applicants note that none of the cited references, alone or in combination, are asserted as teaching or suggesting applicants' compositions containing a pegylated erythropoietin glycoprotein (former claims 20-21, 23-25, 44-50, etc.). Thus, the pegylated erythropoietin glycoprotein-containing compositions are clearly allowable.

Conclusion

In view of the above amendments and the foregoing remarks, it is respectfully submitted that the instant application is in condition for allowance and prompt allowance of the application is solicited.

Respectfully submitted,



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